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Biphasic temporal pattern in exercise capacity after myocardial infarction in the rat: relationship to left ventricular remodeling

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Trueblood, Nathan A., Patrick R. Inscore, Daniel Brenner, Daniel Lugassy, Carl S. Apstein, Douglas B. Sawyer, and Wilson S. Colucci. Biphasic temporal pattern in exercise capacity after myocardial infarction in the rat: relationship to left ventricular remodeling. *Am J Physiol Heart Circ Physiol* 288: H244–H249, 2005. First published September 9, 2004; doi:10.1152/ajpheart.00042.2004.—After myocardial infarction (MI), there is progressive left ventricular (LV) remodeling and impaired exercise capacity. We tested the hypothesis that LV remodeling results in structural and functional changes that determine exercise impairment post-MI. Rats underwent coronary artery ligation ($n = 12$) or sham ($n = 11$) surgery followed by serial exercise tests and echocardiography for 16 wk post-MI. LV pressure-volume relationships were determined using a blood-perfused Langendorff preparation. Exercise capacity was 60% of shams immediately post-MI ($P < 0.05$) followed by a recovery to near normal during *weeks 5–8*. Thereafter, there was a progressive decline in exercise capacity to ±40% of shams ($P < 0.01$). At both 8 and 16 wk post-MI, fractional shortening (FS) was reduced and end-diastolic diameter (EDD) was increased ($P < 0.01$). However, neither FS nor EDD correlated with exercise at 8 or 16 wk ($r^2 < 0.12$, $P > 0.30$). LV septal wall thickness was increased at both 8 ($P = 0.17$ vs. shams) and 16 wk ($P = 0.035$ vs. shams) post-MI and correlated with exercise at both times ($r^2 \geq 0.50$ and $P \leq 0.02$ at 8 and 16 wk). Neither end-diastolic volume nor maximum LV developed pressure at 16 wk correlated with exercise capacity. Exercise capacity follows a biphasic time course post-MI. An immediate decrease is followed by an early recovery phase that is associated with compensatory LV hypertrophy. Subsequently, there is a progressive decrease in exercise capacity that is independent of further changes in LV volume or contractile function.

cardiac hypertrophy; exercise capacity; cardiac function; echocardiography

AFTER A MYOCARDIAL INFARCTION (MI), there is progressive left ventricular (LV) remodeling that is characterized by LV chamber dilation and contractile dysfunction (17, 19). Maximal exercise capacity also decreases post-MI (1, 13, 18, 22). Both the extent of LV remodeling and the impairment in exercise capacity correlate with clinical outcomes in patients with chronic heart failure (5, 7). However, relatively little is known about the relationship between LV remodeling and exercise capacity post-MI. It is possible that LV remodeling is an important determinant of the exercise impairment that occurs after MI. For example, in patients with chronic heart failure due to systolic dysfunction the changes in LV volume, fractional shortening and mass are predictive of exercise capacity (7). On the other hand, exercise capacity often correlates poorly or not at all with central hemodynamics, systolic function, or ventricular volumes in cross-sectional studies (8, 9, 13, 22, 23). Thus the role of LV remodeling in the determination of exercise impairment post-MI is not clear.

We tested the hypothesis that LV remodeling, as reflected by changes in LV structure and function, is a major determinant of exercise impairment post-MI. As an approach to this thesis, we measured maximal exercise capacity on a treadmill at weekly intervals for 16 wk in rats after MI caused by coronary ligation. Correlations were measured between exercise capacity and *1*) echocardiographic measurements of LV size and function at 8 and 16 wk post-MI and *2*) systolic and diastolic pressure-volume relationships measured by the isovolumic Langendorff method at 16 wk post-MI.

METHODS

Animals. Male Wistar rats weighing 225–250 g were housed in a temperature-controlled environment, exposed to a 12:12-h light-dark cycle, and given a standard diet of rat chow and water ad libitum. Experimental protocols were approved by the Institutional Animal Care and Use Committee at Boston University.

Surgical procedure. The animals were randomized to coronary artery ligation (MI) or a sham operation without ligation (sham) as previously described (12, 20). Rats were anesthetized with pentobarbital sodium (45 mg/kg, intraperitoneal injection), intubated, and ventilated with a rodent ventilator (model 386, Harvard Apparatus). The heart was exposed by a left lateral thoracotomy, and the pericardial sac was removed. The left main coronary artery was visualized and ligated with a 5-0 silk suture. Ligation of the coronary artery was confirmed by noting the pallor of the LV wall. To obtain a range of infarction sizes, the location of the coronary ligation varied between 1 and 4 mm distal to its origin between the pulmonary trunk and left atrial appendage. Without exception, distal ligations resulted in small infarct sizes (as determined by histology) and proximal ligations resulted in large infarctions. The chest wall, individual muscles, and skin were sutured separately, and the animal was allowed to recover. Sham-operated rats underwent the same surgical procedures except for the coronary artery ligation.

Exercise protocol. Maximum exercise capacity was measured using a rodent treadmill equipped with an electric motivator grid (Columbus Instruments) as previously described (12). Animals were familiarized with running on the treadmill before surgery. The treadmill was set at a constant incline of 15°. The initial speed was 15 m/min and was increased by 1 m/min every minute. Exercise capacity was measured once per week for the entire 16-wk study. Total exercise time was recorded as the elapsed time to exhaustion and then converted to distance. Exhaustion was determined by an observer blinded to surgery group (sham or MI) and was defined as the point at

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which the animals could not keep pace with the treadmill and no longer avoided the electrical stimulus.

Echocardiography. At 8 and 16 wk post-MI, two-dimensional and M-mode echocardiographic measurements were obtained on nonexercise days. Animals were lightly anesthetized with pentobarbital sodium (20 mg/kg ip), and their chests were shaved. All echocardiographic measurements were obtained using a Hewlett-Packard Sonos 5500 equipped with a 12-MHz vector array probe. End-diastolic diameter (EDD) and end-systolic diameter (ESD) were measured digitally from the frames with the largest and smallest dimensions. The precise phase of the cardiac cycle was confirmed with a simultaneously recorded electrocardiogram. Dimensions were averaged from three cardiac cycles to obtain the value used for each animal. Fractional shortening (FS) was calculated as (EDD − ESD)/EDD.

Pressure-volume relationships in isolated hearts. At the 16-wk endpoint, animals were killed, and their hearts were rapidly isolated. LV diastolic and systolic pressure-volume relationships were obtained by the isovolumic Langendorff method as previously described (12, 20). After the hearts were isolated, the aortic root was canulated, and the coronary arteries were perfused at a constant pressure of 80 mmHg. The perfusate consisted of Krebs-Henseleit buffer supplemented with bovine red blood cells (adjusted to a final hematocrit of 40%) and albumin. LV pressures were monitored via a polyvinyl chloride balloon attached to a small cannula that was inserted through the left atrium into the LV. After pressure-volume assessment, the hearts were arrested in diastole by infusion of potassium chloride and perfusion fixed with formalin at an end-diastolic pressure of 10 mmHg.

Infarct size determination. Infarct size was measured from paraffin-embedded histological sections taken of the formalin-fixed tissue after pressure-volume relationship assessment (19, 20). Four equally spaced short-axis sections were taken to obtain representative samples from the entire vertical length of the LV. The internal and external total LV circumferences and the infarcted portions of the circumference were measured for each of these four sections. The percentage of the LV circumference that consisted of infarcted tissue was then averaged for each section, and each of the four sections were then averaged together, as originally described by Pfeffer et al. (17, 19).

Data analysis. All values are shown as means ± SE. Differences between two independent variables were assessed using an unpaired *t*-test and changes within groups at two time points were assessed using paired *t*-tests. *P* values ≤0.05 were considered statistically significant. ANOVA for repeated measures, followed by Student-Newman-Keuls post tests, was used for serial exercise data.

RESULTS

Infarct size and mortality. MI size ranged from 4% to 38% of the LV, with an average of 26 ± 3%. Survival in sham-operated animals was 100% ($n = 11$). In the infarcted animals, survival was 60% at 24 h postsurgery ($n = 12$ survivors). There was one death at 6 wk post-MI. All results presented are for the animals surviving the full 16 wk (sham, $n = 11$; MI, $n = 10–11$). Lung and liver wet-to-dry weight ratios were not different between the two groups [P = not significant (NS)].

Exercise capacity. After surgery, the maximal exercise capacity of the MI group showed an immediate decrease to ≈60% of sham exercise capacity ($P \leq 0.01$ vs. shams; Fig. 1). The exercise capacity of the MI group remained between 60% and 70% of the sham group levels for the first 4 wk postsurgery ($P < 0.05$ vs. shams). During *weeks 5–9*, however, exercise capacity in the post-MI group recovered to ≈90% of that in the sham group (P = NS vs. shams). Subsequently, there was a progressive decrease between *weeks 10* and *16* in the MI group. At 16 wk, exercise capacity had decreased to 42% of that in the sham group ($P < 0.01$ vs. shams).

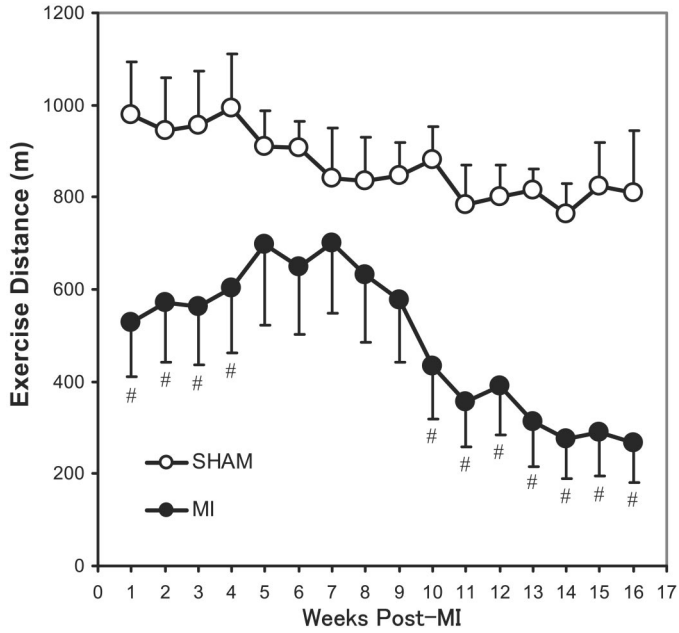

Fig. 1. Changes in maximal exercise capacity (distance run) over time in rats after myocardial infarction (MI; solid circles, $n = 11$) or a sham operation without ligation of the coronary artery (open circles, $n = 11$). Maximal exercise capacity was measured using a progressive treadmill protocol to exhaustion as per METHODS. #$P < 0.05$.

MI size is an important determinant of LV remodeling and post-MI exercise capacity (2). To determine whether MI had an effect on post-MI exercise capacity, exercise capacity was compared in animals with infarcts above and below the group mean infarct size (22%). We found that these post hoc-derived groups had qualitatively similar temporal patterns of exercise limitation post-MI; both were significantly different from the sham group at the beginning and end of the 16-wk study, and both groups came to within 1SD of the exercise distance of shams at *week 8*. However, the decreased sample size of these groups segregated according to infarct size limits the statistical power of between MI size group comparisons.

In vivo LV function by echocardiography. In infarcted rats, LV EDD increased an average of 26% at 8 wk post-MI ($P \leq 0.001$ vs. shams) but did not change between *weeks 8* and *16* (Fig. 2). LV FS decreased ≈40% in the MI group at 8 wk ($P \leq 0.001$ vs. shams) but exhibited no further change between *weeks 8* and *16* (Fig. 2). Compared with shams, there was a nonsignificant increase (12 ± 6%) in septal wall thickness in the MI group at 8 wk ($P = 0.17$ vs. shams), a trend that reached significance by 16 wk post-MI (24 ± 6%, $P < 0.05$ vs. shams; Fig. 2).

In the infarcted animals, neither FS nor EDD correlated with exercise capacity at 8 or 16 wk (Fig. 3, *A–D*). There was, however, a significant positive relationship between septal wall thickness and exercise capacity at both 8 and 16 wk (Fig. 3, *E* and *F*).

Ex vivo LV function in isolated hearts. The end-diastolic pressure-volume relationship was shifted rightward in infarcted hearts ($P < 0.0001$; Fig. 4). The LV end-diastolic volume at 5 mmHg was doubled in post-MI rats (0.63 ± 0.05 ml in post-MI

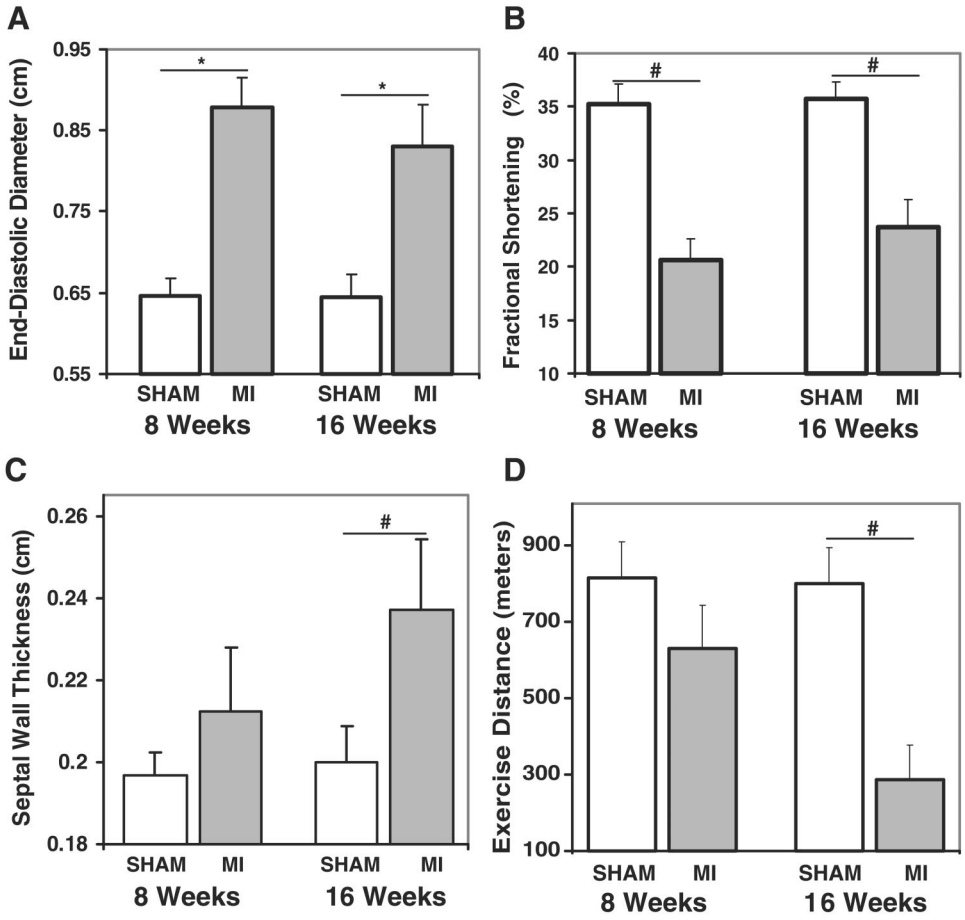

Fig. 2. Left ventricular (LV) end-diastolic diameter (*A*), LV fractional shortening (*B*), septal wall thickness (*C*), and exercise distance (*D*) measured at 8 and 16 wk post-MI; $n = 11$ in both groups. Fractional shortening was calculated from echocardiographic measurements of end-diastolic and end-systolic diameter, as described in METHODS. $*P < 0.001$; $\#P < 0.01$.

vs. 0.30 ± 0.04 ml in shams, $P < 0.0001$). The LV developed pressure-volume relationship was shifted right and downward in infarcted animals ($P < 0.01$; Fig. 4). Maximum LV developed pressure was decreased in infarcted hearts (124 ± 7 mmHg in post-MI hearts vs. 136 ± 5 mmHg in sham hearts, $P = 0.08$). Neither LV end-diastolic volume at 5 mmHg nor LV maximum developed pressure correlated with exercise capacity in the infarcted animals (Fig. 5).

DISCUSSION

The goal of this study was to test the hypothesis that LV remodeling is a determinant of exercise impairment post-MI. There were two major findings. First, the time course of exercise impairment was biphasic. Maximum exercise capacity decreased immediately post-MI but improved to levels approaching those in sham-operated animals between *weeks 5* and *9*. Subsequently, there was a progressive decrease from *week 10* through the end of the study on *week 16*, at which time exercise capacity had decreased markedly to only ≈40% of that in the sham group. The second new finding was that septal wall hypertrophy predicted exercise capacity at both 8 and 16 wk, whereas neither LV dilation nor contractile function, measured in vivo or ex vivo, correlated with exercise capacity.

Time course of exercise impairment post-MI. Relatively little is known about the temporal changes in exercise capacity post-MI. An important feature of the present study is that exercise capacity was measured serially in the same animals for 16 wk post-MI. Most previous studies of exercise capacity in post-MI rats have measured exercise function at only a single time point (25) or have used a cross-sectional design in which different cohorts of animals were studied at each time point (2). Using a cross-sectional approach, Bech et al. (2) found that the time course of exercise impairment post-MI in rats was related to infarct size. In animals with small infarcts (<20%) exercise capacity was reduced at *weeks 1*, *3*, and *7* but normal at *weeks 9* and *13*. In rats with larger infarcts (>20%), exercise capacity was consistently reduced at all times (2). In contrast, we found that the time course of exercise impairment post-MI in animals with small or large MIs showed a similar temporal pattern.

Exercise capacity and LV remodeling. A surprising finding was that exercise impairment did not correlate with LV dilation or systolic dysfunction. By 8 wk post-MI, there was evidence of LV remodeling with both chamber dilation and decreased systolic function. However, neither LV volume nor fractional shortening correlated with exercise capacity, which was normalized at 8 wk. Although LV volume and fractional shortening remained constant between 8 and 16 wk, there was a marked progressive deterioration in exercise capacity. Thus exercise impairment did not correlate with these commonly used measures of LV remodeling post-MI.

Compensatory hypertrophy and exercise capacity. In contrast to the lack of correlation with LV dilation and contractile dysfunction, there were robust positive correlations between

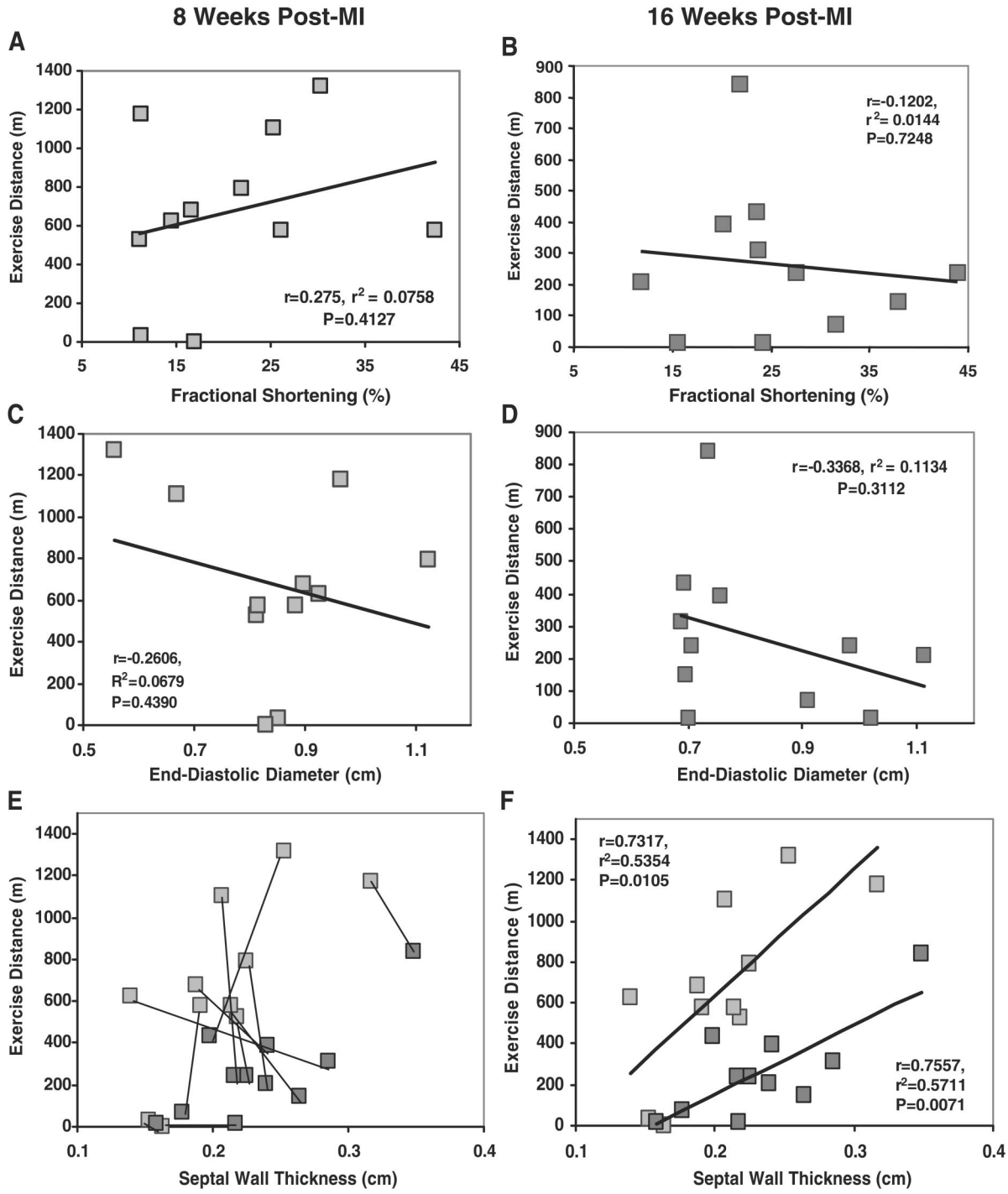

Fig. 3. Relationships between maximal exercise capacity and fractional shortening (*A* and *B*), LV end-diastolic diameter (*C* and *D*), and septal wall thickness (*E* and *F*) measured 8 and 16 wk post-MI. Eight-week data points are light shaded squares, and 16-wk data points are dark shaded squares. In *E*, the 8- and 16-wk data points are connected for each individual; $n = 11$ in both groups.

exercise capacity and septal wall thickness at both 8 and 16 wk post-MI. It is interesting that this relationship persisted at 16 wk, despite the fact that exercise capacity had decreased markedly over the same time period. Because MI in this model is confined to the LV free wall, septal wall thickness reflects hypertrophy of noninfarcted myocardium that is remote from the infarct. Better exercise capacity in animals with more septal hypertrophy suggests that this was an important compensatory response that may have contributed to the early recovery of exercise capacity between 5 and 9 wk post-MI. Likewise, the progressive decrease in exercise capacity after 9 wk occurred despite further septal hypertrophy, which continued to correlate strongly with exercise capacity at 16 wk. These observations suggest that hypertrophy of the remote myocardium exerts a beneficial effect on exercise capacity at both 8 and 16 wk post-MI but that hypertrophy alone is not sufficient to

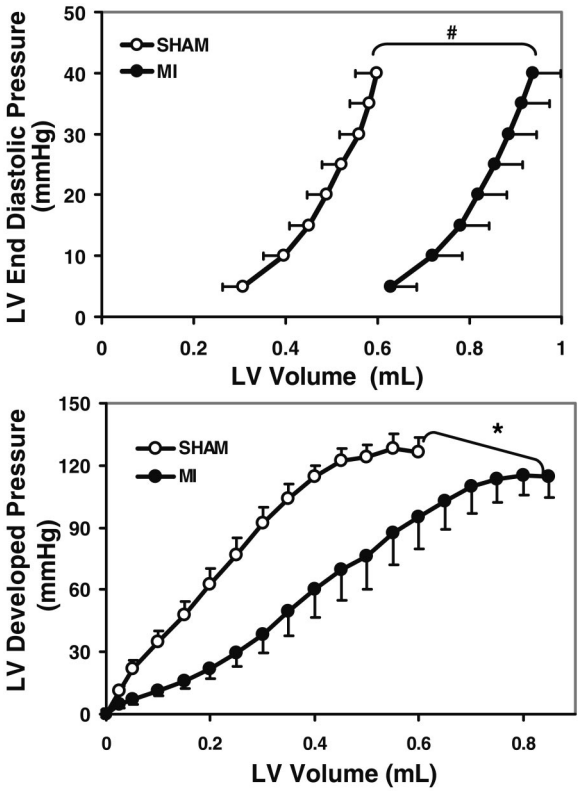

Fig. 4. LV pressure-volume end-diastolic (*top*) and end-systolic relationships (*bottom*) measured in isolated hearts using the isovolumic, balloon in LV Langendorff method. There were 10 hearts in each group. *$P < 0.0001$; #$P < 0.01$.

maintain exercise capacity in the face of other ongoing changes between 9 and 16 wk post-MI.

These data do not identify the mechanism responsible for progressive exercise impairment between *weeks 9* and *16*. There are several possible mechanisms behind the exercise diminution late post-MI in our study, including changes in cardiac/hemodynamic function, skeletal muscle properties, peripheral vascular responsiveness, and/or ventilatory function changes. Because patients with heart failure have attenuated heart rate and blood pressure responses to exercise (9) due to postsynaptic desensitization of β-adrenergic receptors (6), it is possible that there was a progressive adrenergic receptor desensitization late post-MI in the rats in our study. However, it is also possible that changes in skeletal muscles associated with heart failure contributed to the progressive decline in exercise capacity in our rats. Specifically, it has also been shown that skeletal muscles become progressively weaker with heart failure (4), due to changes in calcium handling and force production of myocytes (24), and also due to skeletal muscle cell atrophy (10, 15) and apoptosis (14). Related to these changes in skeletal muscle are alterations in blood flow to the periphery. Specifically, McAllister et al. (16) demonstrated a decrease in the vascular flow capacity to high oxidative muscle fibers, and Ceiler et al. (3) showed decreased nitric oxide production and vascular hyporeactivity in rats post-MI. Accordingly, it is possible that progressive changes in blood flow to skeletal muscles and/or progressive changes in skeletal muscle properties contributed to the post-MI exercise capacity time course seen in our study. Finally, diaphragm strength is reduced (11) and alveolar gas exchange is impaired at rest and during exercise with heart failure (21). In summary, there are a number of changes associated with heart failure. It may be valuable to determine which changes are occurring progressively in association with the changes in exercise capacity post-MI. It is possible that a combination of the changes discussed above are responsible for the progressive exercise intolerance late post-MI.

Limitations. We cannot exclude the possibility that other measures of systolic (e.g., force-frequency relationship) or diastolic function (e.g., filling velocities) might have correlated with exercise performance. A limitation of this study is that the procedure of inducing the range of MI sizes resulted in variation in the location of infarcts, from the hearts with small MIs (infarct only on the apical LV free wall) to the hearts with larger MIs (infarct from apex to base of the LV free wall). It is also possible that larger (e.g., >40%) MIs would yield a different time profile of exercise dysfunction and might exhibit relationships between exercise and LV remodeling that were not evident in this study. Finally, it is possible that further pathological remodeling, which might occur beyond 16 wk, is an important determinant of late changes in exercise capacity.

Summary. These data demonstrate that progressive deterioration in exercise capacity post-MI can occur independent of changes in LV structure and function. Elucidating the noncardiac factors that contribute to exercise impairment in this model may thus improve our understanding of the factors that determine exercise capacity in heart failure. These data further suggest that hypertrophy of the noninfarcted LV serves an important compensatory role that helps to support exercise

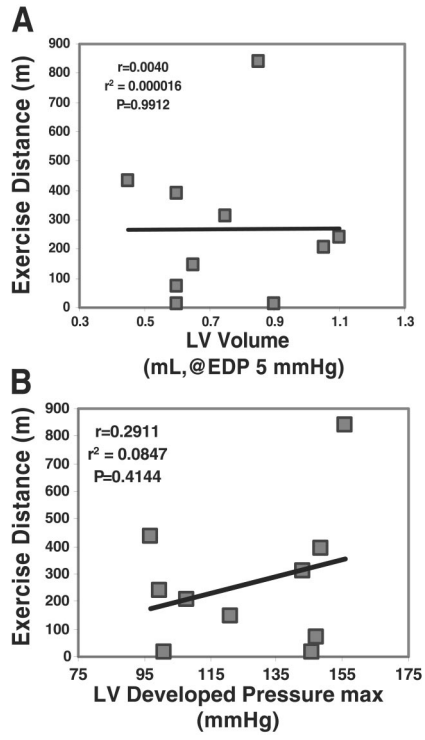

Fig. 5. Relationships between maximal exercise capacity and LV end-diastolic volume (*A*) or LV maximal developed pressure (*B*) as measured in the isolated hearts at 16 wk post-MI, as per Fig. 4; $n = 10$.

function. This latter finding raises the intriguing possibility that interventions that increase the extent of compensatory hypertrophy post-MI might improve exercise capacity.

GRANTS

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